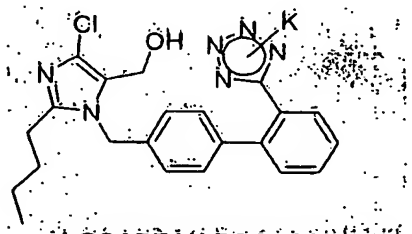
FIELD OF THE INVENTION:

This invention relates to a process for the preparation of losartan potassium and its polymorphic form I.

BACKGROUND OF THE INVENTION:

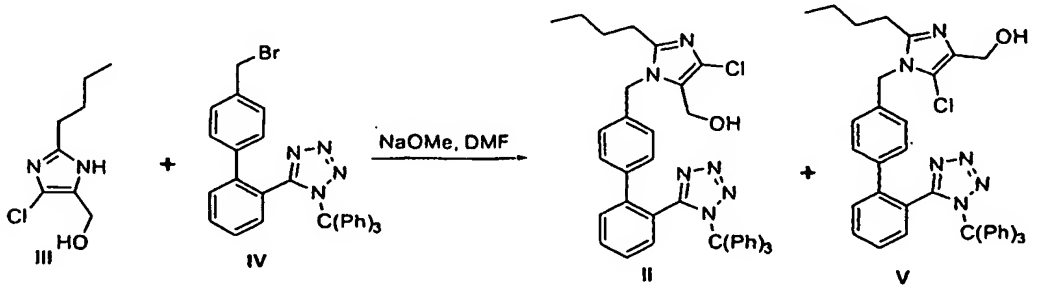
2-butyl-4-chloro-1- {[2'- (1H- tetrazol-5-yl) [1, 1'-biphenyl]- 4 -yl] methyl}- 1*H* -imidazole-5-methanol commonly known as Losartan, is useful in the treatment of hypertension as an AT_1 selective angiotensin II antagonist. Losartan is formulated as its potassium salt (I).



LOSARTAN POTASSIUM (I)

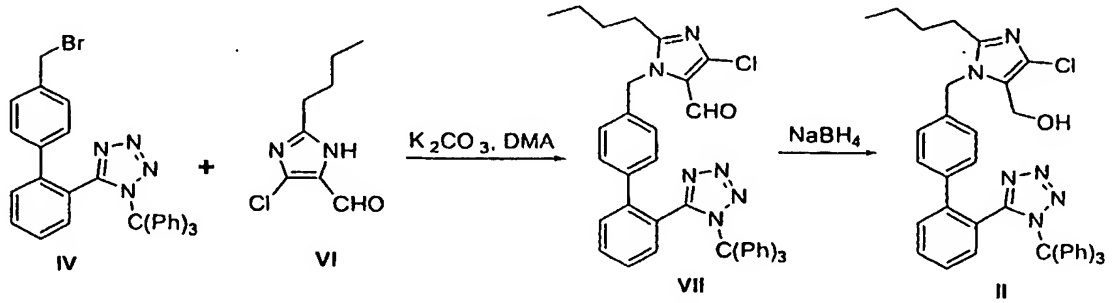
Losartan is generally prepared from 2-Butyl-4-chloro-5- (hydroxymethyl)-1-[[2'-[(triphenylmethyl) tetrazol-5-yl] biphenyl-4-yl] methyl] imidazole, commonly referred as Trityl Losartan (II). Several methods for the preparation of trityl losartan are known in literature and the following paragraphs briefly describe them.

EP 253310 discloses a process, wherein 2-n-butyl-4-chloro-1H-imidazolyl-5-methanol (III) is coupled with 5-(4'-bromomethyl-1, 1'-biphenyl-2-yl)-2-triphenylmethyl-2H-tetrazole (IV) in N, N-dimethylformamide as solvent in presence of sodium methoxide as the base to furnish trityl losartan. The other bases that have been claimed are sodium hydride, alkali metal carbonates such as sodium carbonate and potassium carbonate and amine bases such as triethyl amine and pyridine.



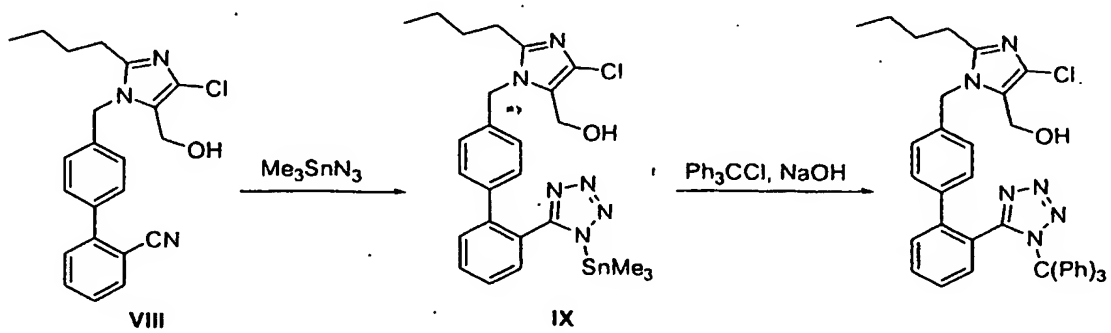
The coupling reaction results in a mixture of trityl losartan and its regio isomer (V). These are separated by column chromatography.

US patents 5,130,439 and 5,310,928 disclose a method for coupling (IV) and (VI) in N,N-dimethylacetamide solvent in the presence of anhydrous potassium carbonate as base. The imidazole aldehyde (VI) gives predominantly the desired regio isomer (VII). The intermediate VII is then reduced with sodium borohydride to furnish the trityl losartan. The product is isolated by extraction into toluene from aqueous N, N-dimethylacetamide, concentration of the toluene solution and crystallization using ethyl acetate or ethanol as solvent. The synthesis steps are depicted as follows.



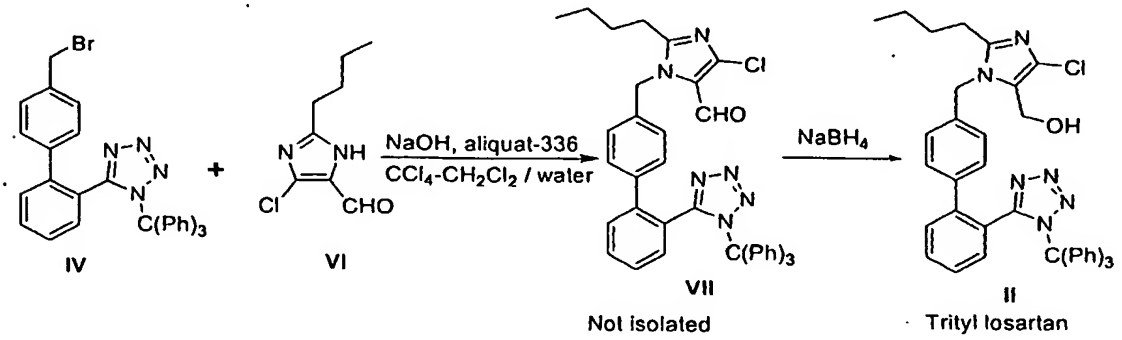
In a process published in *J. Med. Chem.* (1991), 34, 2525-2547, Losartan is prepared by coupling (III) and (IV) in N.N-dimethylformamide in the presence of sodium methoxide. The desired compound is isolated after vacuum distillation of solvent followed by extractive work-up. The resultant product mixture is purified by chromatography.

The US Patents 5,138,069, 5,128,355 and 5,155,118 describe a process for the preparation of losartan, wherein the tetrazole ring of losartan is formed by reacting 1-((2'-cyanobiphenyl-4-yl) methyl)-2-butyl-4-chloro-5-hydroxymethylimidazole with trimethyltin azide. The reaction results in trimethylstannyl substituted tetrazole compound, which is then reacted with trityl chloride and sodium hydroxide.

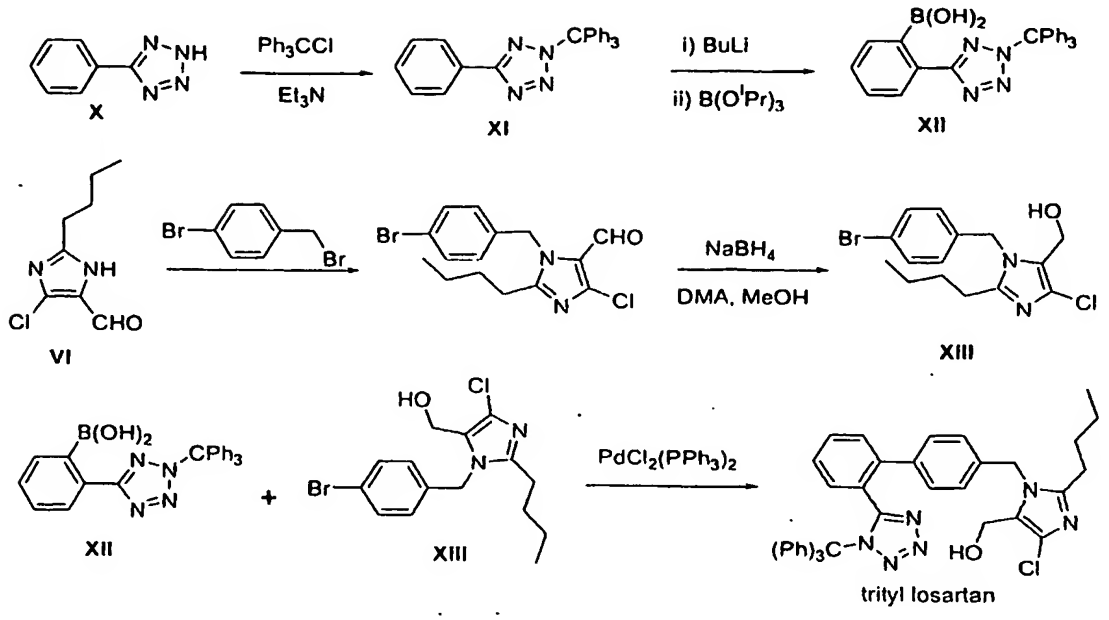


The trityl losartan thus formed is treated with 3.4N hydrochloric acid in methanol at about 10°C to give losartan.

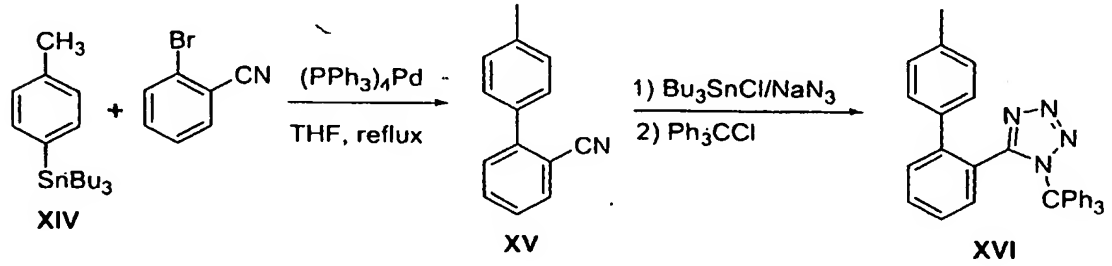
The US Patents 5,138,069, 5,128,355 and 5,155,118 also disclose another process for making trityl losartan, where in the coupling between IV and VI is carried out in a biphasic solvent system comprising of chlorinated solvent and water. The reaction is carried out at room temperature in presence of sodium hydroxide as the base and aliquat 336 as the phase transfer catalyst. The resulting intermediate VII is then reduced *in situ* with sodium borohydride to furnish trityl losartan.



Patent No. 5,206,374, 5310928 and 5962500 disclose another process for preparing losartan in which 5-phenyltetrazole (X) is converted into the boronic acid coupling partner (XII) for the Suzuki reaction by tritylation of phenyltetrazole with trityl chloride in presence of a non-nucleophilic base, ortho metalation with n-butyl lithium, followed by reaction with triisopropylborate. 2-n-butyl-4-chloro-1H-imidazole-5-carboxaldehyde (VI) is alkylated with 4-bromobenzylbromide, followed by reduction of the aldehyde with sodium borohydride to yield the other Suzuki coupling partner (XIII). The product of Suzuki coupling is trityl losartan. This process is published in *J. Org. Chem.* (1994), *59*, 6391-6394.



European patents EP 470,794 and EP 470,795 describe a method for the manufacture of biphenyl carbonitriles (XVI). These patents also describe a method of preparation of trityl losartan by coupling of intermediates (III) and (IV) employing the procedure described in EP 253,310.



Losartan potassium exhibits polymorphism. Several polymorphic forms have been prepared and characterized. The following paragraphs briefly describe various polymorphs.

US patent 5,608,075 discloses the polymorphic forms of losartan, wherein the trityl losartan is deprotected with H_2SO_4 in 50:50 acetonitrile:water and the free acid is treated with KOH solution. The aqueous solution containing losartan potassium is added slowly to a refluxing azeotropic mixture of cyclohexane/iso propanol and the ternary azeotrope cyclohexane/iso propanol/water is distilled till the water content of the pot is less than 0.05%. The white crystalline solid thus obtained is polymorphic form-I, which is characterized by DSC, XRD and IR. Polymorphic form-II is prepared by heating form-I in a DSC cell. This process is also described in US 5,859,258.

US patent 6,710,183 discloses the synthesis of losartan potassium starting from trityl losartan, wherein trityl losartan is reacted in an alcohol of formula R-OH (where R is C_1 to C_4 straight chain alkyl group) with 0.1 to 1 equivalent KOH. Losartan potassium thus formed is isolated after crystallizing out by changing the solvent to an aprotic or weakly protic solvent. The alcohol used is preferably methanol and the protic dipolar solvent used for the crystallization of the final product is preferably acetonitrile or straight or branched chain or cyclic aliphatic hydrocarbons.

EP 1294712 (WO 02/094816) discloses the process to manufacture losartan potassium form-I, wherein trityl losartan or losartan is suspended in a solvent and KOH is added to obtain a clear solution, which is then concentrated under reduced pressure to remove most of the solvent. An anti solvent is added to crystallize losartan potassium. The solvents to prepare losartan potassium include methanol, ethanol, and butanol but preferably the salt formation is carried out in methanol. Anti solvent is selected from common solvents such as ethyl acetate, acetonitrile, toluene and acetone, but the preferred anti solvent is acetone.

US application 2004/0006237 (WO 03/048135) relates to novel amorphous and novel crystalline forms III, IV, V of losartan potassium and the processes for their preparation. The patent also discloses novel processes for preparing losartan potassium forms I and II. The preparation of amorphous losartan includes the step of dissolving losartan potassium in a solvent to form a solution and distilling the solvent form the solution to dryness. Losartan form III (hydrated) is obtained by exposing losartan potassium amorphous or form I to an atmosphere having high relative humidity. Losartan potassium form IV is obtained by treating a saturated solution of losartan potassium in ethanol with methylene chloride. Losartan form V is obtained by treating a saturated solution of losartan potassium in ethanol with hexane. Losartan potassium form II is obtained by adding a saturated solution of losartan potassium in ethanol to xylene to form a mixture and evaporating ethanol from the mixture. Losartan form I is obtained by treating a saturated solution of losartan potassium in ethanol or iso propanol, with less soluble solvent like ethyl acetate, toluene, acetone, methyl ethyl ketone, methylene chloride, acetonitrile, dimethyl carbonate or hexane.

US application 2004/0034077 (WO 03/093262) discloses a process for preparing losartan and losartan potassium, wherein trityl losartan is treated with an acid in a diluent comprising a ketone. Especially preferred liquid ketones are acetone, methyl ethyl ketone and methyl isobutyl ketone, and acetone being the most preferred. Acids, which have been found suitable, include hydrochloric acid, sulphuric acid, acetic acid, trifluoroacetic acid, hydrobromic acid and formic acid. After the trityl losartan has been substantially converted to losartan, reaction mixture is

basified. Preferred bases are alkali metal hydroxides and alkoxides. After addition of the base, the liquid ketone is evaporated under vacuum. After separation of triaryl methyl alcohol the residue is acidified to yield losartan. Free losartan is suspended in an alcohol and treated with a solution of potassium ions. Finally losartan potassium is precipitated from the alcohol. The alcohol is selected from the group consisting of isopropyl alcohol, butyl alcohol and isobutyl alcohol. The potassium ion solution is prepared by dissolving potassium iso propoxide, potassium butoxide and potassium iso butoxide or potassium hydroxide in the diluent.

US application 2004/0097568 discloses a process for preparing form III of losartan potassium, wherein trityl losartan is treated with aqueous solution of potassium hydroxide in methanol to obtain losartan potassium. The solvent is evaporated under vacuum and traces of water are removed as an azeotrope with toluene. Methanol and carbon are added to the resulting mixture. The carbon is filtered and the methanol is distilled. The resulting mixture is cooled to 20-25°C to obtain crystalline form III losartan potassium.

The processes described above for the preparation of trityl losartan have several disadvantages. These include use of highly toxic and hazardous reagents like trialkyl tin azides, expensive and sensitive catalysts like tetrakis (triphenyl phosphine) palladium or highly reactive bases like butyl lithium. Some of the reactions are conducted at very low temperatures. Many of these procedures use water miscible solvents like N, N-dimethyl formamide or tetrahydrofuran. The reactions carried out in a biphasic solvent system comprising of chlorinated solvent and water in the presence of a phase transfer catalyst results in very low yields. The literature procedures for the detritylation of trityl losartan are generally carried out in presence of an acid or a base. The isolation of free losartan from the acid catalyzed reaction involves extensive work up. The free losartan obtained is then crystallized from mixture of solvents to obtain form I. Therefore there exists a need for an improved process that eliminates the disadvantages of the prior art process for the synthesis of losartan potassium.

SUMMARY OF THE INVENTION

The present invention relates to the disclosure of an efficient and cost effective method of synthesis of losartan potassium comprising the preparation of trityl losartan by reacting N-triphenylmethyl-5- [4'-(bromomethyl) biphenyl-2-yl] tetrazole [IV] and 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [VI] in a biphasic solvent system comprising water and an organic solvent under phase transfer catalysis in alkaline conditions, followed by *in situ* reduction using sodium borohydride. The trityl losartan thus obtained is suspended in an alcoholic solvent and heated to temperature of about 35 to reflux temperature of the solvent in the absence of acid or

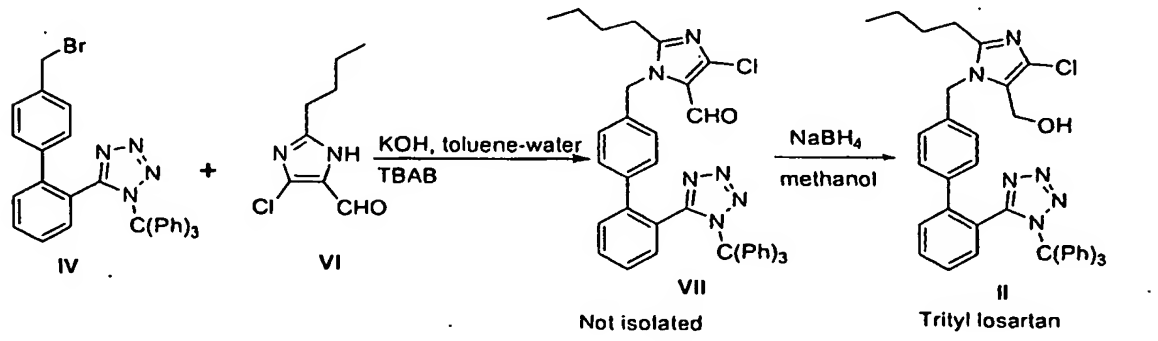
base catalysts to deprotect trityl losartan. The solvent is distilled off under reduced pressure to leave a residue that is then taken up in an organic solvent. The precipitated free losartan is filtered off and free losartan is suspended in an organic solvent capable of forming azeotrope with water and treated with aqueous potassium hydroxide solution. The solution is distilled to remove water as an azeotrope till moisture content of the mixture is less than 0.1%. Upon cooling losartan potassium crystallizes in polymorphic form-I and is isolated by filtration.

Alternatively, the residue obtained after distillation of alcoholic solvent is taken up in an organic solvent and treated with aqueous potassium hydroxide solution to dissolve losartan as its potassium salt. The layers are separated and water is removed from the aqueous solution as an azeotrope with an organic solvent as before.

DETAILED DESCRIPTION OF THE INVENTION:

The aim of the present invention is to develop an improved process that eliminates the disadvantages of the prior art process for synthesis of Trityl Losartan and also to provide a novel process to prepare polymorphic form I of Losartan potassium.

The present invention provides an improved process that eliminates the disadvantages of the prior art processes for synthesis of trityl losartan and also to eliminate extensive purification procedures to separate the regio isomer. According to the invention, the coupling reaction between intermediates (IV) and (VI) is carried out in presence of a base and phase transfer catalyst in an aqueous/organic biphasic solvent system where organic solvent is selected from toluene, xylene, pentane, heptane, octane, cyclohexane etc. Preferably the reaction is carried out in toluene. The reaction temperature varies from 25 °C to reflux temperature of the solvent, preferably from 80 to 100°C.



The phase transfer catalyst is selected from any of the tetra alkyl ammonium halides or tetra alkyl phosphonium halides. The preferred catalyst is tetra butyl ammonium bromide because of its easy availability and low cost. The quantity of the catalyst used varies from about 0.1 to 5mol% with about 2mol% being most suitable. The base employed is selected from alkali metal hydroxides such as lithium hydroxide; sodium hydroxide or potassium hydroxide the preferred base is potassium hydroxide in about 100mol% to 300mol% with about 130mol% being most suitable. The reaction is carried out from ambient temperature to reflux temperature of the solvent and it generally takes 2-10 hours to go to completion. Typically, the reaction is conducted at 80-90°C for about 3-4 hours. After the reaction has proceeded to a desired stage as judged by HPLC analysis, the reaction mixture is diluted with water and allowed to settle. The aqueous phase is removed and the organic phase is washed with water to remove any traces of phase transfer catalyst and base. The organic phase is then diluted with an alcohol selected from any of C1-C4 alcohols, preferably methanol and reduced with sodium borohydride in quantities ranging from 0.2 equivalents to 2 equivalents. Typically, about 0.5 equivalent of sodium borohydride is used. The reduction is carried out in a temperature range of about -10 to +20°C with 0-5°C being most appropriate. The alcohol acts as a protonating source during the reduction of the aldehyde VII to trityl losartan. When the reaction has proceeded to a desired stage, it is quenched by addition of water. The desired product precipitates from the reaction mass. It is then isolated by filtration. The product thus isolated is about 96% pure and can be utilized for the production of Losartan potassium directly without any further purification. Thus in a "one pot" operation, synthesis of trityl losartan is achieved.

The present invention also provides novel methods for preparing losartan potassium form-I. According to the literature procedures, the detritylation is generally carried out in presence of an acid or a base. The cleavage of the trityl group is achieved with strong acid such as hydrochloric acid or sulphuric acid and the desired losartan potassium is isolated after extensive work up. In case of the base catalyzed reaction, trityl losartan is treated with potassium hydroxide in methanol to obtain losartan potassium *in situ*.

Surprisingly we found that losartan can be easily obtained by heating trityl losartan in an alcoholic solvent, in the absence of an acid or a base catalyst. The alcoholic solvent is selected from any C1-C4 alcohols. The preferred solvent is methanol. The reaction is carried out at ambient temperature to reflux temperature of the solvent and it generally takes 2-12 hour for completion. Typically the reaction is conducted at reflux temperature for 4-5 hour. After completion of the reaction, alcoholic solvent is distilled off under reduced pressure. The resulting mass containing trityl methyl ether (by product) and free losartan is suspended in an organic

solvent (A). The organic solvent (A) is selected from the group consisting of toluene, ethyl acetate, acetone, acetonitrile and methylene chloride. The preferred solvent is toluene. The trityl methyl ether being freely soluble in toluene is extracted into solvent where as the free losartan remains insoluble. The resulting suspension is filtered and washed with toluene to obtain free losartan. The free losartan obtained is suspended in another organic solvent (B) that is capable of forming an azeotrope with water and treated with aqueous potassium hydroxide solution to obtain a clear solution. The quantity of base used varies from about 0.98 - 1 equivalent with respect to the starting material, with 1 equivalent being most suitable.
The solution is distilled to remove water as an azeotrope till moisture content of the mixture is less than 0.1%. Upon cooling losartan potassium crystallizes in polymorphic form-I and is isolated by filtration.

Thus a suspension of trityl losartan in methanol is refluxed for about 4-5h. The solid slowly dissolves and deprotection takes place. After completion of the reaction, methanol is distilled off under reduced pressure. The resulting mass is taken up in toluene in which trityl methyl ether is freely soluble. The free losartan remains insoluble and is filtered. The free losartan thus obtained is suspended in a solvent capable of forming an azeotrope with water and treated with concentrated solution of aqueous potassium hydroxide. The mixture is stirred to obtain a clear solution. The solvents can be selected from acetonitrile, acetone, 2-butanone, ethyl acetate and toluene. The preferred solvent is acetonitrile. The solution is distilled to remove water as an azeotrope (boiling point 76.5°C). The distillation is continued till the moisture content of the solution is less than 0.1%. The mass is cooled to room temperature and crystalline solid thus obtained is filtered and found to be form I as established by extensive analytical methods.

In another embodiment of this invention, the free losartan is suspended in acetonitrile and treated with concentrated solution of aqueous potassium hydroxide. The mixture is stirred to obtain a clear solution. The solution is diluted with isopropyl ether and the resulting solution is distilled to remove water as ternary azeotrope (59°C). The ternary azeotrope has a lower boiling point than the binary azeotrope. The distillation is continued till the moisture content of the solution is less than 0.1%. The crystalline solid thus obtained is filtered and found to be form I as established by extensive analytical methods.

In another embodiment of this invention, a suspension of trityl losartan in methanol is refluxed for about 4-5 hours. After completion of the reaction, methanol is distilled off under reduced pressure. The resulting mass is suspended in toluene and treated with aqueous potassium hydroxide solution. The mixture is stirred to obtain a clear solution. The aqueous layer containing

losartan potassium is separated. Fresh toluene is added and water is removed as an azeotrope with toluene (85°C). The distillation is continued till the moisture content of the solution is less than 0.1%. The crystalline solid thus obtained is filtered and found to be form I.

In another embodiment of this invention, trityl losartan is treated with ethanolic potassium hydroxide solution. The mixture is diluted with water to precipitate trityl methyl ether. The precipitated trityl methyl ether is filtered. Resulting solution is further diluted with 2-butanone. The solution is distilled to remove water as a ternary azeotrope (73.2°C). When the solution is dry the potassium salt crystallizes. The crystalline solid thus obtained is filtered and found to be form I as established by extensive analytical methods.

The present invention is illustrated with following examples without limiting, the scope of the invention.

Example-1

Preparation of trityl losartan:

To a solution of N- (triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl] tetrazole [1.0Kg; 1.61mol], 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [0.28 kg; 1.501 mol] and tetra butyl ammonium bromide [0.01 kg; 0.03mol] in 5L toluene is added 0.6L of a 3M solution of potassium hydroxide in water. The reaction is vigorously stirred and refluxed for 3.5 hour. The progress of the reaction is monitored by HPLC. The reaction mass is cooled to room temperature and is allowed to settle. The lower aqueous layer is discarded and the toluene layer is washed with water (2L). The toluene layer is diluted with methanol (0.6 L) and cooled to 0°C. Sodium borohydride (0.031 kg, 0.837 mol) is added in lots maintaining the temperature below 5 °C. Progress of the reaction is monitored by HPLC. The reaction is stopped by addition of 3L water. The precipitated solid is filtered, washed with toluene (0.5 L) and dried to give Trityl Losartan

Yield: 0.9 kg. [90.2%]

^{1}H NMR ($CDCl_3$): δ 9.73(s, 1H,); 7.92 (m, 1H); 7.51-6.81 (m, 22H); 5.45(s, 2H); 2.49(t, 2H); 1.64(q, 2H); 1.28 (sextet, 2H) and 0.86 (t, 3H)

Example-2

Preparation of trityl losartan:

To 50 ml of xylene, N- (triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl] tetrazole [9.0 g; 0.0164 mol], 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [2.83 g; 0.015mol], tetra butyl ammonium bromide [0.217 g; 0.0006 mol] and a solution of potassium hydroxide (1.21 g in 15 ml of water) are added. The reaction is vigorously stirred and refluxed for 3.5 hours. The progress of the reaction is monitored by HPLC. The reaction mass is cooled to room temperature and is

allowed to settle. The lower aqueous layer is discarded and the xylene layer is washed with water (50 ml). Further it is diluted with methanol (20 ml) and cooled to 0 °C. Sodium borohydride (0.3367 g, 0.0089 mol) is added in lots maintaining the temperature below 5 °C. Progress of the reaction is monitored by HPLC. The reaction is stopped by addition of water (30 ml). The precipitated solid is filtered, washed with xylene (10 ml) and dried.

Yield: 8.8 g [74.01%].

Example-3

Preparation of trityl losartan:

To 50 ml of toluene, N- (triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl] tetrazole [9.0 g; 0.0164 mol], 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [2.83 g; 0.015mol], tetra butyl ammonium bromide [0.217 g; 0.0006 mol] and a solution of potassium carbonate (3.1 g in 15 ml of water) are added. The reaction is vigorously stirred and refluxed for 3.5 hours. The progress of the reaction is monitored by HPLC. The reaction mass is cooled to room temperature and is allowed to settle. The lower aqueous layer is discarded and the toluene layer is washed with water (50 ml). Further it is diluted with methanol (20 ml) and cooled to 0 °C. Sodium borohydride (0.3367 g, 0.0089 mol) is added in lots maintaining the temperature below 5 °C. Progress of the reaction is monitored by HPLC. The reaction is stopped by addition of water (30 ml). The precipitated solid is filtered, washed with toluene (10 ml) and dried.

Yield: 8.0 g [66%]

Example-4

Preparation of trityl losartan:

To 50 ml of toluene, N- (triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl] tetrazole [9.0 g; 0.0164 mol], 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [2.83 g; 0.015mol], Aliquat-336 [0.14 g; 0.00035 mol] and a solution of potassium hydroxide (1.25 g in 15 ml of water) are added. The reaction is vigorously stirred and refluxed for 3.5 hours. The progress of the reaction is monitored by HPLC. The reaction mass is cooled to room temperature and is allowed to settle. The lower aqueous layer is discarded and the toluene layer is washed with water (50 ml). Further it is diluted with methanol (20 ml) and cooled to 0 °C. Sodium borohydride (0.31 g, 0.0081 mol) is added in lots maintaining the temperature below 5 °C. Progress of the reaction is monitored by HPLC. The reaction is stopped by addition of water (30 ml). The precipitated solid is filtered, washed with toluene (10 ml) and dried.

Yield: 6.7 g [62%].

Example-5

Preparation of trityl losartan:

To 50 ml of toluene, N- (triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl] tetrazole [9.0 g; 0.0164 mol], 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [2.83 g; 0.015mol], cetrimide [0.03 g; 0.00035 mol] and a solution of potassium hydroxide (1.29 g in 15 ml of water) are added. The reaction is vigorously stirred and refluxed for 3.5 hours. The progress of the reaction is monitored by HPLC. The reaction mass is cooled to room temperature and is allowed to settle. The lower aqueous layer is discarded and the toluene layer is washed with water (50 ml). Further it is diluted with methanol (20 ml) and cooled to 0 °C. Sodium borohydride (0.311 g, 0.0082 mol) is added in lots maintaining the temperature below 5 °C. Progress of the reaction is monitored by HPLC. The reaction is stopped by addition of water (30 ml). The precipitated solid is filtered, washed with toluene (10 ml) and dried.

Yield: 7.9 g [68%].

Example-6

Preparation of trityl losartan:

To 50 ml of methylene chloride, N- (triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl] tetrazole [10.2 g; 0.018 mol], 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [3.4 g; 0.018 mol], tetra butyl ammonium bromide [0.2618 g; 0.00081 mol] and a solution of potassium hydroxide (1.45 g in 15 ml of water) are added. The reaction is vigorously stirred and refluxed for 12 hours. The progress of the reaction is monitored by HPLC. The reaction mass is cooled to room temperature and is allowed to settle. The upper aqueous layer is discarded and the methylene chloride layer is washed with water (50 ml). Further it is diluted with methanol (20 ml) and cooled to 0 °C. Sodium borohydride (0.3367 g, 0.009 mol) is added in lots maintaining the temperature below 5 °C. Progress of the reaction is monitored by HPLC.

The solvent is removed under reduced pressure and the residue obtained is dissolved in toluene 30 ml. Distillation is continued until the temperature reaches 110° C. The reaction mass is cooled to 40°C and then diluted with 15 ml of ethyl acetate and 25 ml of n-heptane. The reaction mixture is further cooled to 0-10°C and stirred for about 10 minutes. The slurry obtained is filtered. Washed with cold toluene/ethyl acetate.

Yield: 7.5 g [62%].

Example-7

Preparation of free losartan:

Trityl losartan (50g; 0.075mol) is suspended in methanol (250ml). The resulting mixture is refluxed for 4-5 hours to obtain a clear solution. Methanol is distilled off under reduced pressure. The resulting mass is suspended in toluene (250ml) and stirred at 45-50°C for about 15 min. The free losartan, which is insoluble, is filtered and washed with toluene.

Yield: 28g (88%)

Example-8

Preparation of losartan potassium form I:

Trityl losartan (200g; 0.3mol) is suspended in methanol (1L). The resulting mixture is refluxed for 4-5 hours to obtain a clear solution. Methanol is distilled off under reduced pressure. The resulting mass is suspended in toluene (1L) and treated with a solution of potassium hydroxide (85%, 20g; 0.3 mol) in water (500ml). The mixture is stirred for 15-20 min. to obtain a clear solution. The aqueous layer containing losartan potassium is separated. Fresh toluene (1.2L) is added to the aqueous solution. The resulting mixture is distilled to remove water as an azeotrope. The distillation is continued till the moisture content of the solution is less than 0.1%. The crystalline solid thus obtained is filtered and found to be form I as established by extensive analytical methods.

Yield: 125g (92%)

Example-9

Preparation of losartan potassium form I:

A suspension of free losartan (25g; 0.059mol) in acetonitrile (150ml) is treated with a solution of potassium hydroxide (85%, 3.9g; 0.059 mol) in water (20ml). The mixture is stirred for 15-20 min. to obtain a clear solution. The solution is diluted with isopropyl ether (150ml). The resulting solution is distilled to remove water as an azeotrope. The distillation is continued till the moisture content of the solution is less than 0.1%. The crystalline solid thus obtained is filtered and found to be form I as established by extensive analytical methods.

Yield: 25g (92%)

Example-10

Preparation of losartan potassium form I:

A suspension of free losartan (25g; 0.059mol) in acetonitrile (500ml) is treated with a solution of potassium hydroxide (85%, 3.9g; 0.059 mol) in water (15ml). The mixture is stirred for 15-20 min. to obtain a clear solution. The resulting solution is distilled to remove water as an azeotrope. The distillation is continued with drop wise addition of acetonitrile (500ml), till the moisture content of the solution is less than 0.1%. The crystalline solid thus obtained is filtered and found to be form I as established by extensive analytical methods.

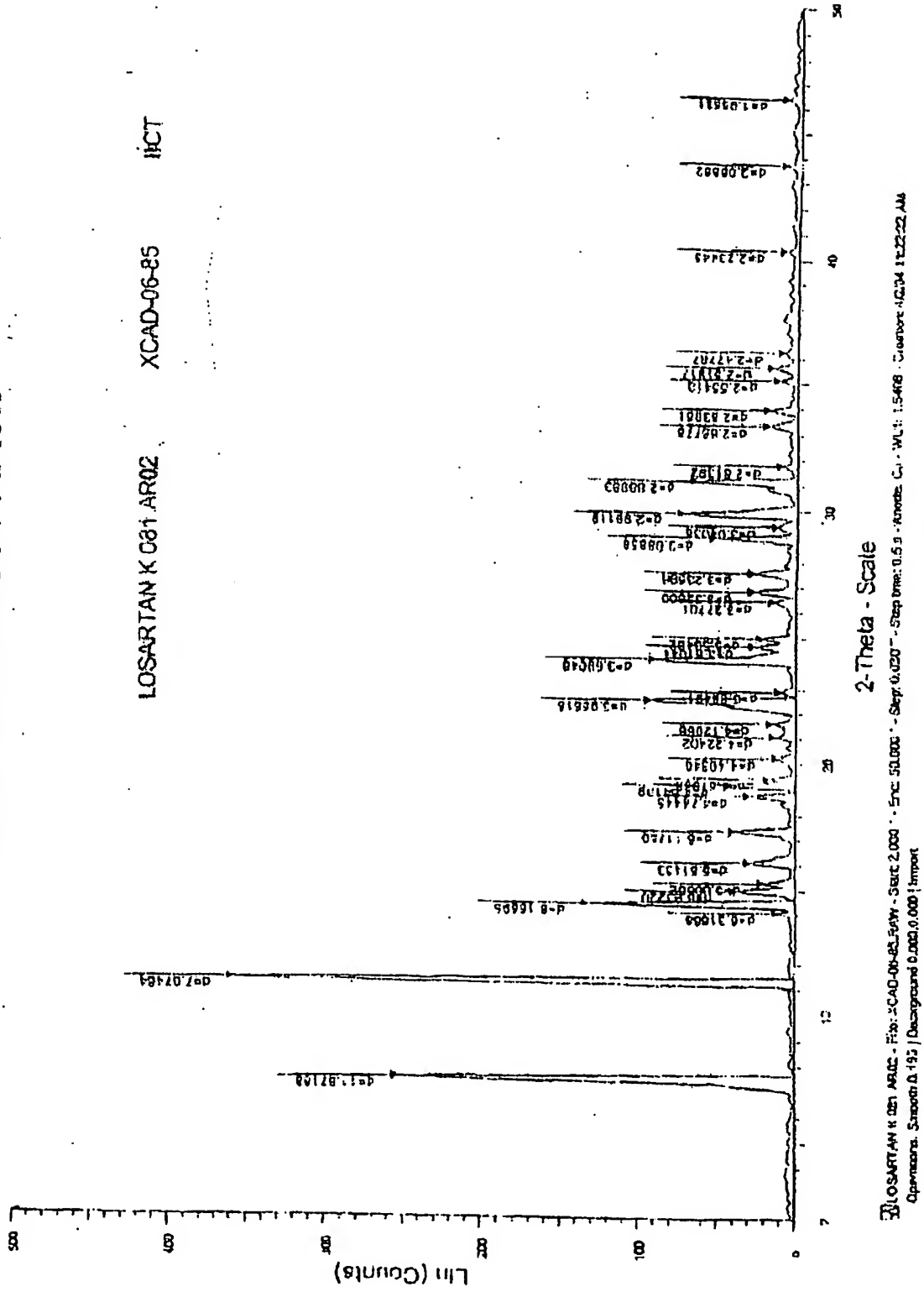
Yield: 25g (92%)

Example-11

Preparation of losartan potassium form I:

A suspension of trityl losartan (10g; 0.015mol) in ethanol (60ml) is treated with potassium hydroxide (85%, 1g; 0.015mol). The resulting mixture is refluxed for 24 hours. Cooled the mixture to room temperature and diluted with water (5ml). The precipitated trityl methyl ether is filtered. The filtrate containing losartan potassium is further diluted with methyl ethyl ketone (150 ml). The resulting solution is distilled to remove water as an azeotrope. When the solution is dry the potassium salt crystallizes. The crystalline solid thus obtained is filtered and found to be form I as established by extensive analytical methods.

Yield: 5.2g (82%)



Angle 2-Theta °	d value[16] Angstrom	Intensity % %
7.441	11.87168	70.7
11.227	7.87464	100.0
14.009	6.31668	2.5
14.377	6.15595	36.7
14.922	5.93230	10.3
15.251	5.80502	5.2
16.060	5.51433	7.8
17.314	5.11750	10.3
18.688	4.74445	7.6
19.106	4.64139	11.0
19.368	4.57935	4.3
20.150	4.40340	2.7
21.015	4.22402	3.2
21.548	4.12066	3.8
22.455	3.95618	25.7
22.877	3.88421	2.4
24.096	3.69046	24.8
24.638	3.61044	6.9
24.964	3.56402	5.7
26.371	3.37701	3.6
26.783	3.32600	7.2
27.542	3.23596	7.2
28.884	3.08858	14.2
29.353	3.04036	3.1
29.846	2.99119	19.9
31.140	2.86983	17.6
31.775	2.81392	2.2
33.308	2.68778	4.7
33.936	2.63951	4.5
35.106	2.55413	2.9
35.610	2.51917	4.0
36.224	2.47787	2.1
40.332	2.23445	1.9
43.724	2.06862	2.0
46.401	1.95531	2.0

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CPRI

TEST REPORT

Test report No :DMDPOL040 003 Dated 06.04.2004
Test requested by : M/s Cadila Pharmaceuticals Limited, Dhanvanthri Kshetra, A Research Laboratory of Cadila Pharmaceuticals Ltd., IISc Campus, Bangalore - 560 012.
Reference No. & Date : Nil, Dt. 01.04.04
No. of Samples : One only
Identification of the Sample : Received the sample in a glass bottle labelled as Losartan K 081AR02

Test Conducted : DSC Studies
Tests in accordance with : General guidelines of ASTM D 3417 – 99

Sl. No.	Particulars of the Test	Results		
		Onset, ^{0}C	Peak Temperature, ^{0}C	Endo - Enthalpy, J/g
	DSC Studies of			
1.	Losartan K 081AR02	271.00	273.62	- 76.13
	[Instrument Used : Differential Scanning calorimeter Make : Mettler-Toledo, Model : DSC 821 °, Type of Sample Pan: Aluminium Pan , Test Temperature : 40 to 360 ^{0}C Heating Rate : 10 deg/min Atmosphere : Nitrogen, Flow Rate - 50 ml/min.]			

Test Engineer